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ΚΥΠΡΙΑΚΟ ΓΡΑΦΕΙΟ ΔΙΠΛΩΜΑΤΩΝ ΕΥΡΕΣΙΤΕΧΝΙΑΣ
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ΑΡΙΘΜΟΣ ΔΗΜΟΣΙΕΥΣΗΣ
ΓΡΑΦΕΙΟΥ ΔΙΠΛΩΜΑΤΩΝ ΕΥΡΕΣΙΤΕΧΝΙΑΣ
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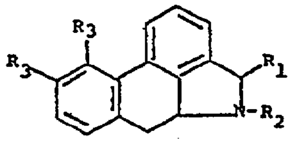
(54) 4,5,5a,6-tetrahydrodibenz[cd,f]indoles

(57) The 4,5,5a,6-tetrahydrodibenz[cd,f]indoles of formula



I

wherein either R_1 and R_2 independently are ethyl or *n*-propyl radicals and the R_3 substituents are the same and are hydroxy or acyloxy radicals, in racemic form having the relative configuration 4R*,5aS* or in optically active isomer form having the absolute configuration 4S,5aR, are useful as central dopaminergic stimulent agents.

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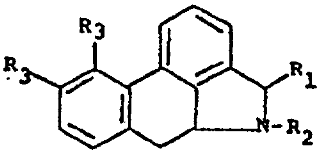
SPECIFICATION

Heterocyclic compounds, their preparation and pharmaceutical compositions containing them

The present invention relates to phenanthrene derivatives, their preparation and pharmaceutical compositions containing them.

Belgian patent n° 877 169 describes a class of 4,5,5a,6-tetrahydro-dibenz[cd,f]indole derivatives having stimulant activity on central dopaminergic receptors. All the compounds specifically exemplified which have alkyl groups attached to positions 4 and 5, contain as one alkyl group a methyl group. It has been now surprisingly found that a group of (4R*,5aS*)-4,5,5a,6-tetrahydro-dibenz[cd,f]indole derivatives having ethyl and *n*-propyl groups in the 4 and 5 positions, which are nowhere specifically described or suggested in this patent, possess a particularly interesting pharmacological profile, inter alia, long duration of action and/or notable potency as central dopaminergic agents and good tolerability.

In accordance with the invention there are provided compounds of formula I,



I

wherein
R_1 and R_2 independently, are ethyl or *n*-propyl radicals, and
the R_3 substituents are the same and are hydroxy or acyloxy radicals,
in racemic form having the relative configuration 4R*,5aS*, or in optically active isomer form having the absolute configuration 4S,5aR.

The acyloxy radicals are conveniently radicals of formula

R_a—CO—O—

in which R_a is an alkyl radical, (C_{3-7})cycloalkyl, a phenyl radical or a 5- or 6-membered heterocyclic ring.

When R_a is an alkyl radical, this may conveniently contain 1—17 carbon atoms, preferably 1 to 7 carbon atoms, and may be straight chain or branched chain.

R_a may be a substituted alkyl radical, containing in the alkyl chain conveniently 1—5 carbon atoms. Conveniently it is a monosubstituted alkyl radical. The substituents may be, e.g., carboxy, hydroxy, amino, (C_{1-4})alkylamino, (C_{1-4})alkoxy, di-(C_{1-4})alkylamino, halogen, (C_{1-4})alkylthio, phenoxy, a phenyl radical, 1-pyrrolidinyl, piperidino or morpholino, and conveniently a phenyl radical. R_a may also be e.g. an alkyl radical containing in the alkyl chain 1—4 carbon atoms and substituted by (C_{3-7})cycloalkyl.

When R_a is a phenyl radical or alkyl substituted by a phenyl radical, the phenyl radical may be unsubstituted or contain 1, 2 or 3 identical or different substituents, selected, for example, from halogen, trifluoromethyl, (C_{1-4})alkyl, (C_{1-4})alkoxy, (C_{1-4})alkylthio and di-(C_{1-4})alkylamino, or a methylenedioxy group. Preferably the phenyl ring is mono- or disubstituted.

When R_a is an alkyl substituted by a phenyl radical, R_a is preferably a benzyl radical. The phenyl ring may bear substituents selected, for example, from halogen, (C_{1-4})alkyl, (C_{1-4})alkoxy or (C_{1-4})alkylthio.

When R_a is a heterocyclic ring, this is suitably a heterocycle containing oxygen, nitrogen or sulfur as sole heteroactom, e.g. pyridine, thiophene or furan.

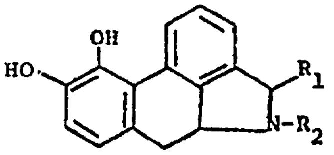
Preferably R_a is (C_{1-7})alkyl; (C_{3-6})cycloalkyl; unsubstituted phenyl; phenyl mono- or disubstituted by chlorine, fluorine, trifluoromethyl, (C_{1-4})alkyl or (C_{1-4})alkoxy; unsubstituted benzyl; or benzyl mono- or disubstituted by chlorine, fluorine, (C_{1-4})alkyl or (C_{1-4})alkoxy.

Halogen may signify chlorine, bromine or fluorine, preferably chlorine or fluorine.

In a group of compounds, R_1 is *n*-propyl and R_2 is ethyl. In another group of compounds, R_1 and R_2 are the same and signify ethyl or *n*-propyl. Preferably in the compounds of formula I the R_3 substituents are hydroxy. The preferred compounds are the (4S,5aR) optical isomers.

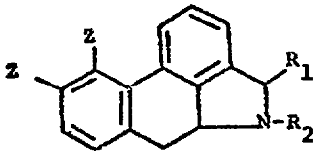
More particularly the invention provides a process for the production of compounds of formula I, which comprises

a) producing a compound of formula Ia



Ia

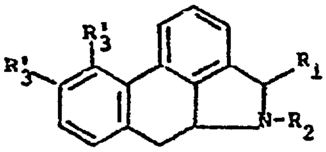
wherein R_1 and R_2 are as defined above, by splitting the ether groups Z of a compound of formula II



II

wherein R_1 and R_2 are defined above and Z is a splittable ether group, in racemic form having the relative configuration 4R*,5aS*, or in optically active isomer form having the absolute configuration 4S,5aR, or

b) producing a compound of formula Ib



Ib

wherein R_1 and R_2 are defined above and the radicals R_3' are identical acyloxy radicals, by acylating a compound of formula Ia in racemic form having the relative configuration 4R*,5aS* or in optically active isomer form having the absolute configuration 4S,5aR.

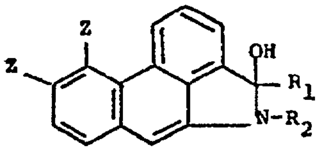
The ether splitting process according process a) may be effected in conventional manner for splitting ether groups. For example the reaction may be carried out by treatment of the starting materials with a strong mineral acid, e.g. hydrobromic or hydroiodic acid, at a temperature of at least 100°C, preferably from 100°C to the boiling point of the reaction mixture, especially at about 130°C. The ether group Z is preferably a methoxy radical.

The acylation process according to process b), may be effected in conventional manner for the selective acylation of phenolic groups in the presence of an amine function. For example there may be used, as acylating agent, a functional derivative of an acid such an acid chloride, acid bromide or the acid anhydride. Conveniently the reaction is carried out by reacting an acid chloride in the presence of trifluoroacetic acid at temperatures frofm 20°C to the boiling point of the reaction mixture or in the presence of pyridine at temperature from 0°C to room temperature.

The resulting compounds of formula I may be isolated from the reaction mixture and purified in known manner. The free base forms of compounds of formula I may be converted into acid addition salt forms in conventional manner and *vice versa*. Suitable acids for salt formation are, for example, hydrochloric acid, tartaric acid, di-O,O-p-toluoyl-D- or L-tartaric acid, and hydrobromic acid.

Racemic compounds of formula I may be obtained from racemic starting materials. Optically active isomers of formula I may be obtained from optically active precursors with the configuration (4S,5aR) or from the racemate. The 4S,5aR enantiomer may be obtained from racemate by known methods, for example by fractional crystallization of diastereoisomeric salts, e.g. their salts with (+)-di-O,O-p-toluoyl-D-tartaric acid or (—)-di-O,O-p-toluoyl-L-tartaric acid. Racemic resolution into the optically active isomers may be effected preferably at an early stage in the synthesis, e.g. before splitting of the ether groups.

The starting materials of formula II may be prepared by reducing compounds of formula III

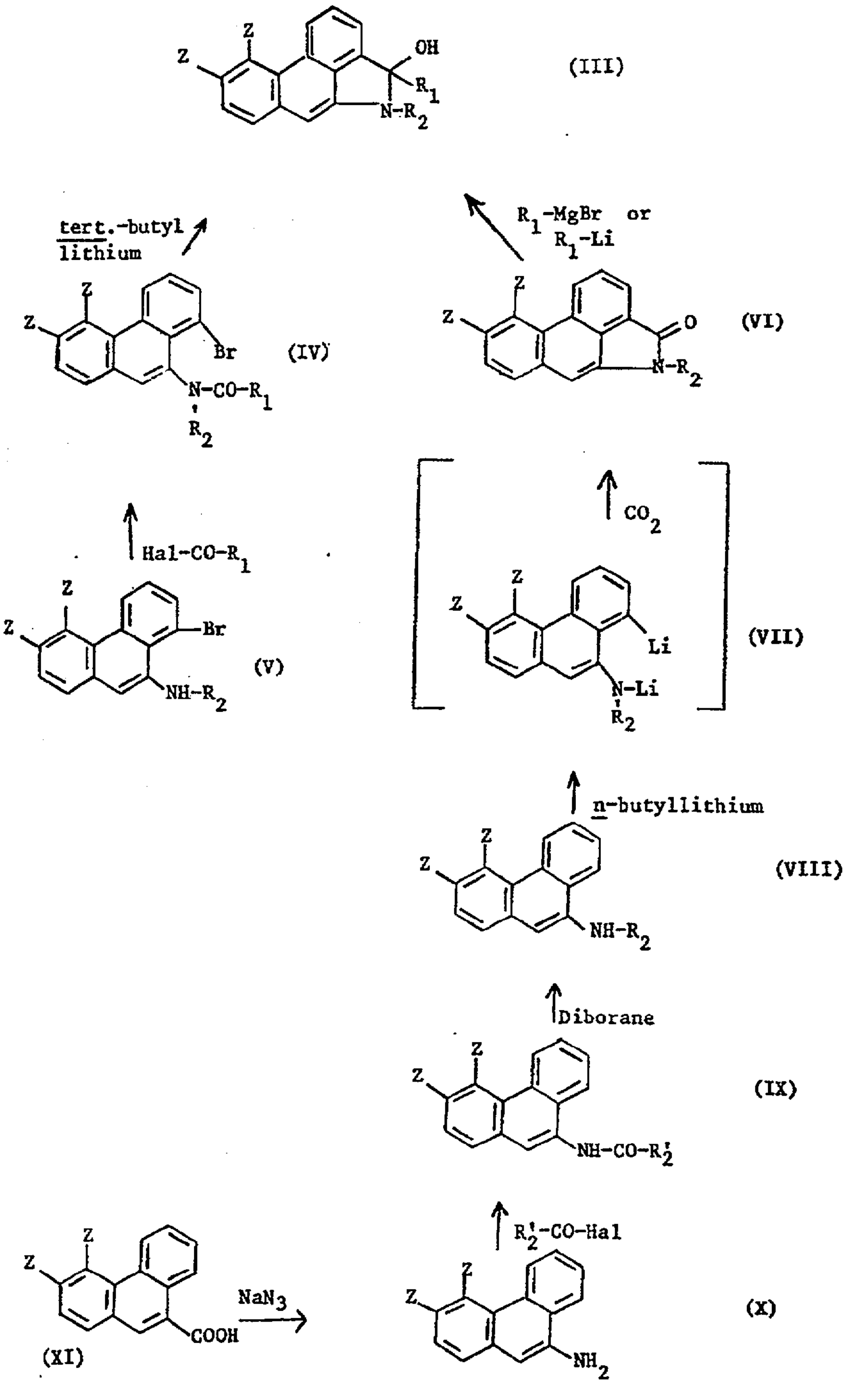


III

wherein R_1, R_2 and R_3 are as defined above.

The reduction may be effected conveniently under acidic conditions suitable for the acidic reduction of enamines or imines, for example with zinc in an aqueous mineral acid, preferably hydrochloric acid, conveniently in the presence of a mercury (II) salt, for example mercury(II) chloride. The reaction may suitably be effected for example in ethanol, and at temperatures from 50°C to the boiling point of the reaction mixture.

Starting materials of formula III may be prepared, for example, according the following reaction scheme:



In the reaction scheme the radicals R_1, R_2 and Z are as defined above and R_2' is methyl or ethyl. The reactions may be carried out in conventional manner and the products of the above reactions may be isolated and purified in known manner.

In the above intermediates the ether groups Z are conveniently methoxy.

Insofar the preparation or any particular starting material is not particularly described, this may be effected in conventional manner. For example the phenanthrene derivatives which are starting materials of formula XI, are described in the Elsevier's Encyclopaedia of Organic Chemistry, vol. 13, Tricyclic compounds, Elsevier Publishing Company Inc. New York (1946).

In the following Examples all temperatures are given in degrees Celsius and are uncorrected.

EXAMPLE 1

a) 9-(N-ethyl-N-butyryl-amino)-3-bromo-3,4-dimethoxy-phenanthrene [compound of formula IV)]

A solution of 50 g (138 mM) 9-ethylamino-8-bromo-3,4-dimethoxy-phenanthrene in 57.5 ml (333 mM) N-ethyl-diisopropylamine and 420 ml methylene chloride is added dropwise, with stirring, under a nitrogen atmosphere over a period of 20 minutes to a solution of 28.8 ml (276 mM) butyryl chloride in 420 ml methylene chloride. During the addition the reaction mixture is maintained at room temperature by cooling in a water bath. The resultant yellow-red solution is then worked up in known manner to afford 9-(N-ethyl-N-butyryl-amino)-8-bromo-3,4-dimethoxy-phenanthrene; M.pt 102—104°.

b) (4RS)-5-ethyl-4,5-dihydo-4-hydroxy-9,10-dimethoxy-4-*n*-propyl-dibenz[cd,f]indole [compound of formula III]

25 g (58.14 mM) of 9-(N-ethyl-N-butyrylamino)-8-bromo-3,4-dimethoxy phenanthrene are dissolved with stirring in 450 ml anhydrous tetrahydrofuran and the solution obtained is cooled to −25° with a bath of methylene chloride and dry ice. 73 ml (116.28 mM) of a 1.7 molar solution of *tert.*-butyl-lithium in pentane are then added dropwise over 4 minutes. Then the temperature of the reaction mixture is allowed to increase to +5° over a period of 30 minutes, the reaction mixture is poured onto 500 ml of a mixture water and ice, extracted three times with, each time, 500 ml methylene chloride, and the organic phases are washed with water, dried and evaporated. After the product is dried in high vacuum, there is obtained (4RS)-5-ethyl-4,5-dihydro-4-hydroxy-9,10-dimethoxy-4-*n*-propyl-dibenz[cd,f]indole in the form of a yellow green foam.

c) (±)-(4R*,5aS*)-5-ethyl-4,5,5a,6-tetrahydro-9,10-dimethoxy-4-*n*-propyl-dibenz[cd,f]indole [compound of formula II]

A suspension of 40.6 g (116 mM) of (4RS)-5-ethyl-4,5-dihydro-4-hydroxy-9,10-dimethoxy-4-*n*-propyl-dibenz[cd,f]indole in 1060 ml ethanol is added with stirring to a suspension of 140 g of zinc dust and 31.6 g (116 mM) of mercury (II) chloride in 1060 ml distilled water (alternatively the zinc dust/mercury chloride may be added to the dibenzindole). The reaction mixture is refluxed, 360 ml of 18% hydrochloric acid are added dropwise over a period of 15 to 20 minutes and the mixture is refluxed overnight with stirring. The reaction mixture is cooled to room temperature, filtered and the zinc amalgam is washed with 500 ml methylene chloride. The filtrate is made alkaline with 1 litre of concentrated NH_4OH and the alkaline phase is extracted once with 1 litre methylene chloride and twice with, each time, 500 ml methylene chloride. The combined organic phases are washed with water, dried and evaporated. The resultant oil is chromatographied on silicagel using methylene chloride with 2% methanol as eluant to give (±)-(4R*,5aS*)5-ethyl-4,5,5a,6-tetrahydro-9,10-dimethoxy-4-*n*-propyl-dibenz[cd,f]indole in form of an oil.

EXAMPLE 2

The (4RS)-5-ethyl-4,5-dihydro-4-hydroxy-9,10-dimethoxy-4-*n*-propyl-dibenz[cd,f]indole obtained in the Example 1b), may also be prepared as follows:

a) 9-amino-3,4-dimethoxy-phenanthrene [compound of formula X]

A mixture of 430 ml (3.08 moles) trifluoroacetic anhydride and 430 ml (5.62 moles) trifluoroacetic acid is added at room temperature under a nitrogen atmosphere to 53.6 g (0.19 mole) 3,4-dimethoxy-phenanthrene-9-carboxylic acid and the mixture is stirred for 10 minutes. After the mixture is cooled to −5°, 15.2 g (0.234 mole) sodium azide are carefully added in solid form, the mixture is stirred for 3 hours at 2°, poured onto ice and the resulting suspension worked up in known manner to give 9-amino-3,4-dimethoxy-phenanthrene as a solid. The hydrochloride melts at over 215° with decomposition.

b) 9-acetylamino-3,4-dimethoxy-phenanthrene [compound of formula IX]

55 ml (0.319 mole) N-ethyldiisopropylamine are added to a solution of 38.2 g (0.151 mole) 9-amino-3,4-dimethoxy-phenanthrene in 200 ml methylene chloride. To the resulting mixture is added dropwise over 200 minutes a solution of 20.8 ml (0.292 mole) acetyl chloride in 250 ml methylene chloride. During the addition, the temperature of the reaction mixture is maintained at 20° by cooling with a ice bath. The reaction mixture is stirred for 14 hours at room temperature and worked up in known manner to afford 9-acetylamino-3,4-dimethoxy-phenanthrene; M.pt. 190—195° after recrystallisation from ether.

c) 9-ethylamino-3,4-dimethoxy-phenanthrene [compound of formula VIII]

34 g (0.124 mole) 9-acetylamino-3,4-dimethoxy-phenanthrene in suspension in 450 ml anhydrous tetrahydrofuran are reduced with 500 ml (0.5 mole) of a molar solution of diborane in anhydrous tetrahydrofuran and worked up in known manner to give 9-ethylamino-3,4-dimethoxy-phenanthrene; M.pt. 94—95°.

d) 4,5-dihydro-9,10-dimethoxy-5-ethyl-4-oxo-dibenz[cd,f]indole [compound of formula VI]

122 ml (0.2 mole) of a 15% solution of *n*-butyl-lithium in hexane are added at 0°, under a nitrogen atmosphere, to a solution of 28.1 g (0.1 mole) of 9-ethylamino-3,4-dimethoxy-phenanthrene in 300 ml anhydrous tetrahydrofuran; the reaction mixture becomes bright red. Dry ice is then added until the colouration disappears: the formation of a solution with yellow-green fluorescence is observed. After the temperature of the reaction mixture is allowed to reach room temperature, the mixture is poured

onto water/ice, extracted three times with methylene chloride and the organic phase dried over sodium sulfate and evaporated. There is thus obtained 4,5-dihydro-9,10-dimethoxy-5-ethyl-4-oxo-dibenz[cd,f]indole which melts at 125—126° (with decomposition) after crystallisation from ether/petroleum ether.

e) (4RS)-5-ethyl-4,5-dihydro-4-hydroxy-9,10-dimethoxy-4-*n*-propyl-dibenz[cd,f]indole [compound of formula III]

2.1 ml (33 mM) of a solution of *n*-propyl-magnesium bromide in ether are added dropwise at room temperature to a solution of 10 g (33 mM) of 4,5-dihydro-9,10-dimethoxy-5-ethyl-4-oxo-dibenz[cd,f]indole in 300 ml anhydrous tetrahydrofuran. After 30 minutes, a solution of ammonium chloride is added, the mixture extracted with methylene chloride and the organic phase dried and evaporated to give (4RS)-5-ethyl-4,5-dihydro-4-hydroxy-9,10-dimethoxy-4-*n*-propyl-dibenz[cd,f]indole in the form of a yellow green foam. [IR Spectrum (CH_2Cl_2): 3540 cm^{-1} (OH)]. The crude product is directly used for the next step.

EXAMPLE 3
(±)-(4R*,5aS*)-5-ethyl-4,5,5a,6-tetrahydro-9,10-dihydroxy-4-*n*-propyl-dibenz[cd,f]indole

20 g (27.66 mM) (±)-(4R*,5aS*)-5-ethyl-4,5,5a,6-tetrahydro-9,10-dimethoxy-4-*n*-propyl-dibenz[cd,f]indole in 200 ml of a 47% aqueous solution of hydrobromic acid are warmed for 6 hours at reflux, at a bath temperature of 150°. After evaporation of the reaction mixture to dryness, the crystalline residue is stirred in acetone and filtered under suction. The precipitate is washed with acetone then with ether and dried under high vacuum. There is thus obtained (±)-(4R*,5aS*)-5-ethyl-4,5,5a,6-tetrahydro-9,10-dihydroxy-4-*n*-propyl-dibenz[cd,f]indole hydrobromide which melts at 200° with decomposition.

The following compounds may be prepared in analogous manner from the appropriate starting materials:

a) (±)-(4R*,5aS*)-4,5-diethyl-4,5,5a,6-tetrahydro-9,10-dihydroxy-dibenz[cd,f]indole (hydrobromide, M.pt >175° with decomposition);
b) (±)-(4R*,5aS*)-4,5,5a,6-tetrahydro-9,10-dihydroxv-4 5-di-*n*-propyl-dibenz[cd,f]indole (hydrobromide, M.pt >190° with decomposition).
c) (±)-(4R*,5aS*)-4-ethyl-4,5,5a,6-tetrahydro-9,10-dihydroxy-5-*n*-propyl-dibenz[cd,f]indole.

EXAMPLE 4
(—)-(4S,5aR)-5-ethyl-4,5,5a,6-tetrahydro-9,10-dihydroxy-4-*n*-propyl-dibenz[cd,f]indole
a) (—)-(4S,5aR)-5-ethyl-4,5,5a,6-tetrahydro-9,10-dimethoxy-4-*n*-propyl-dibenz[cd,f]indole

30 g (89 mM) of (±)-(4R*,5aS*)-5-ethyl-4,5,5a,6-tetrahydro-9,10-dimethoxy-4-*n*-propyl-dibenz[cd,f]indole are dissolved in 300 ml ether and a solution of 35.95 g of (—)-di-O,O-p-toluoyl-L-tartaric acid monohydrate in 300 ml ether is added with stirring. The mixture is further stirred for one hour at room temperature, a total of 1 litre ether being added in portions during this period. The resultant precipitate is filtered off under suction, washed with ethyl acetate until it remains light yellow, and dried.

61.88 g of the crystals obtained from the first crystallisation are dissolved in 1 litre acetone and 300 ml methanol at reflux and the solution is filtered and concentrated until a major part of the product crystallizes out. The mixture is stirred for about 15 minutes, the product is filtered off under suction, washed with ethyl acetate until it remains colourless and dried.

The resulting product is recrystallised in the same manner by using 1.7 litres acetone and 35 ml methanol to give colourless crystals.

The resulting crystals are recrystallised in the same manner, by using 1.2 litres acetone and 60 ml methanol. There is thus obtained (—)-(4S,5aR)-5-ethyl-4,5,5a,6-tetrahydro-9,10-dimethoxy-4-*n*-propyl-dibenz[cd,f]indole (—)-di-O,O-p-toluoyl-L-tartrate in form of colourless crystals which melt at 178—179°; $[\alpha]_D^{20} = -138°$ (c = 0.29 in methanol).

The following compounds may be prepared in analogous manner from the appropriate starting materials:

— (—)-(4S,5aR)-4,5-diethyl-4,5,5a,6-tetrahydro-9,10-dimethoxy-dibenz[cd,f]indole (—)-di-O,O-p-toluoyl-L-tartrate, M.pt 187—189°; $[\alpha]_D^{20} = -138°$ (c = 0.5 in methanol); the racemic starting material is reacted first with (+)-di-O,O-p-toluoyl-D-tartaric acid instead of the L-isomer and the mother liquor obtained on crystallisation is treated with NH_4OH to liberate the base. The base is reacted with (—)-di-O,O-p-toluoyl-L-tartaric acid and the crystals obtained from an ether solution.

— (—)-(4S,5aR)-4,5,5a,6-tetrahydro-9,10-dimethoxy-4,5-di-*n*-propyl-dibenz[cd,f]indole (—)-di-O,O,-p-toluoyl-L-tartrate, M.pt 165—166°; $[\alpha]_D^{20} = -123°$ (c = 0.27 in methanol).

b) (—)-(4S,5aR)-5-ethyl-4,5,5a,6-tetrahydro-9,10-dihydroxy-4-*n*-propyl-dibenz[cd,f]indole

Proceding as described in Example 3, (—)-(4S,5aR)-5-ethyl-4,5,5a,6-tetrahydro-9,10-dihydroxy-4-*n*-propyl-dibenz[cd,f]indole hydrobromide is obtained from the tartrate obtained above under a). It melts above 210°; $[\alpha]_D^{20} = -64°$ (c = 0.245 in methanol).

The corresponding hydrochloride melts at above 185° with decomposition; $[\alpha]_D^{20} = -75°$ (c = 0.28 in methanol).

EXAMPLE 5

The following compounds may be prepared in analogous manner as described in Example 4b) from the appropriate starting materials:

a) (—)-(4S,5aR)-4,5-diethyl-4,5,5a,6-tetrahydro-9,10-dihydroxy-dibenz[cd,f]indole hydrochloride, M.pt. 200° with decomposition; $[\alpha]_D^{20} = -72°$ (c = 0.25 in methanol);
b) (—)-(4S,5aR)-4,5,5a,6-tetrahydro-9,10-dihydroxy-4,5-di-*n*-propyl-dibenz[cd,f]indole hydrochloride, M.pt > 187° with decomposition; $[\alpha]_D^{20} = -58.5°$ (c = 0.35 in methanol).
c) (—)-(4S,5aR)-4-ethyl-4,5,5a,6-tetrahydro-9,10-dihydroxy-5-*n*-propyl-dibenz[cd,f]indole.

EXAMPLE 6

(+)-(4S,5aR)-5-ethyl-9,10-dibenzoyloxy-4,5,5a,6-tetrahydro-4-*n*-propyl-dibenz[cd,f]indole

0.376 ml (3.23 mM) of benzoyl chloride are added dropwise with stirring, over 5 minutes and at a temperature of +5°, to a solution of 600 mg (1.54 mM) of (—)-(4S,5aR)-5-ethyl-4,5,5a,6-tetrahydro-9,10-dihydroxy-4-*n*-propyl-dibenz[cd,f]indole hydrobromide in 5 ml anhydrous pyridine and the reaction mixture is further stirred for 14 hours at room temperature. The mixture is then evaporated to dryness, the residue is dissolved in methylene chloride and the solution is washed first with a mixture of ice and a saturated solution of potassium bicarbonate, and then with water. The aqueous phases are extracted twice with methylene chloride and the combined organic phases are dried and evaporated. The residue is dissolved in methylene chloride and the solution evaporated under high vacuum. The procedure of dissolving the residue in methylene chloride and evaporating is repeated twice more. 550 mg of the resulting product are dissolved in acetone and this solution is added dropwise to a solution of 156 mg L(+)-tartaric acid in acetone. The resultant precipitate is filtered off and dried to give (+)-(4S,5aR)-5-ethyl-9,10-dibenzoyloxy-4,5,5a,6-tetrahydro-4-*n*-propyl-dibenz[cd,f]indole L(+)tartrate; it melts at 161—162° after crystallisation in ethyl acetate/ether; $[\alpha]_D^{24} = +23.5°$ (c = 0.28 in methanol).

The following compounds may be prepared in analogous manner from the appropriate starting materials

— (—)-(4S,5aR)-9,10-diacetoxy-5-ethyl-4,5,5a,6-tetrahydro-4-*n*-propyl-dibenz[cd,f]indole hydrochloride, M.pt >188° (with decomposition); $[\alpha]_D^{20} = -99°$ (c = 0.28 in methanol);
— (—)-(4S,5aR)-5-ethyl-4,5,5a,6-tetrahydro-4-*n*-propyl-9,10-dipropionyloxy-dibenz[cd,f]indole hydrochloride, M.pt >175° (with decomposition); $[\alpha]_D^{20} = -76°$ (c = 0.25 in methanol);
— (—)-(4S,5aR)-9,10-dibutyryloxy-5-ethyl-4,5,5a,6-tetrahydro-4-*n*-propyl-dibenz[cd,f]indole hydrochloride, M.pt >105° (with decomposition); $[\alpha]_D^{20} = -77°$ (c = 0.28 in methanol)
— (—)-(4S,5aR)-5-ethyl-4,5,5a,6-tetrahydro-9,10-diisobutyryloxy-4-*n*-propyl-dibenz[cd,f]indole hydrochloride, M.pt >165° (with decomposition); $[\alpha]_D^{20} = -96°$ (c = 0.29 in methanol).
— (—)-(4S,5aR)-5-ethyl-4,5,5a,6-tetrahydro-4-*n*-propyl-9,10-divaleryloxy-dibenz[cd,f]indole hydrochloride;
— (—)-(4S,5aR)-5-ethyl-4,5,5a,6-tetrahydro-4-*n*-propyl-9,10-dipivaloyloxy-dibenz[cd,f]indole hydrochloride;
— (—)-(4S,5aR)-4,5,5a,6-tetrahydro-9,10-dipropionyloxy-4,5-di-*n*-propyl-dibenz[cd,f]indole, M.pt 115°; $[\alpha]_D^{20} = -76°$ (c = 0.51 in methanol).

In analogous manner to Example 6, the following compounds of formula I wherein R_1 and R_2 are each independently ethyl or *n*-propyl and R_3 is

— acetoxy
— propionyloxy
— butyryloxy
— isobutyryloxy
— valeryloxy
— pivaloyloxy

may be prepared.

The compounds of formula I possess pharmacological activity. In particular, the compounds are indicated for use as central dopaminergic stimulant agents, as indicated by the following standard tests:

The dopaminergic activity of compounds of formula I was studied in the rat according the method described by U. Ungerstedt in Acta Physiol. Scand., Suppl. *367*, 69—93 (1971). 6-hydroxydopamine is unilaterally injected in the substantia nigra which produces, after a week, unilateral degeneration of nigrostriatal pathways. Administration of from about 0.03 to about 1 mg/kg i.p. of the compounds of formula I to these rats leads to a notable turning behaviour of long duration contralateral to the lesion.

The central dopaminergic activity of compounds of formula I has been also confirmed according the following test.

Rats, 180—222 g, are placed in "Perspex" (registered Trade Mark) cylinders of 30 cm diameter on a wire grid floor. After 30 minutes to allow acclimatisation to the cage, the rats are injected with the compound under investigation. The behaviour of the rats is observed for 2 minutes at 30 minutes intervals for 2 hours and then at 60 minutes intervals for total of up to 6 hours. The degree of stereotyped behaviour observed is assessed using a scoring system based on that described by Costall, Naylor and Olley [Euro J. Pharmac. *18*, 83—94 (1972)].

The scores and criteria are as follows:

1. Intermittent sniffing
2. Persistent sniffing, ocassional licking
3. Licking, occasional biting
4. Intense and persistent biting.

Administered i.p. from about 0.03 to about 30 mg/kg animal body weight, the compounds of formula I induce stereotyped sniffing, licking and biting behaviour in the rat.

The compounds are therefore indicated for use as central dopaminergic stimulant agents, for example for treating Morbus Parkinson. For this indication, an indicated daily dose is from about 0.1 to about 20 mg, conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing from about 0.025 to about 10 mg, or in sustained release form.

The compounds of the invention exhibit furthermore anti-depressant activity, as indicated by the inhibition of catalepsy induced by reserpine in mice on s.c. administration of about 0.001 mg to about 1 mg/kg of the compounds and by the inhibition of the catalepsy induced by tetrabenazine in rats on i.p. administration of about 0.2 to about 2 mg/kg of the compounds.

The compounds are therefore indicated for use as anti-depressant agents.

An indicated daily dosage is in the range from about 0.05 to about 2 mg, conveniently given in divided doses 2 to 4 times a day in unit dosage form containing from about 0.01 mg to about 1 mg of the compounds admixed with a solid or liquid pharmaceutical carrier or diluent.

The compounds of formula I exhibit furthermore prolactin secretion inhibition as indicated by the lowering of serum levels of prolactin of the rat after s.c. administration of from about 0.1 to about 1 mg/kg of the compounds, using radio-immunological techniques, e.g. described by Niswender, G.D. et al., Biol. & Med. *130,* 793 (1969) and Neil, J.J. et al., Endocrinology *88*, 548 (1971).

The compounds of formula I are therefore indicated for use as prolactin inhibitors, e.g. in the treatment of conditions involving hyperprolactinemia, such as menstrual dysfunctions, e.g. ammenorrhea and galactorrhea, or hypertension of mammary carcinoma associated with elevated serum prolactin levels, or in the treatment of conditions involving hypogonadism, e.g. infertility or impotence, or in the regulation of post-partem lactation.

An indicated daily dosage is in the range from about 5 to about 50 mg, conveniently given in divided doses 2 to 4 times a day in unit dosage form containing from about 1.25 mg to about 25 mg of the compounds admixed with a solid or liquid pharmaceutical carrier or diluent.

The compounds of the invention exhibit furthermore antipsychotic activity as indicate by the inhibition of the locomotion in mice on s.c. administration of from about 0.001 mg to about 0.1 mg/kg of the compounds and by the dopamine agonistic action on the presynaptic receptors of the rat at doses of from about 1 mg to about 10 mg/kg of the compounds, according the following test.

The dopamine agonistic action of the compounds of formula I on the presynaptic receptors was studied on the rat using the in vivo method described by J. R. Walters and coll. in Naunyn Schmiedeberg's Arch. Pharmacol. *296*, 5—14 (1976). The dopaminergic impulse flow was inhibited pharmacologically by γ-butyrolactone. The activity of the aromatic amino acid decarboxylase was inhibited by hydroxybenzylhydrazine (NSD 1015) and half an hour later the rats were sacrificed. The resulting accumulation of DOPA during 30 minutes in striatal tissue was taken as a measure of the in vivo activity of tyrosine hydroxylase. Administration per os of the compounds reversed the effects of γ-butyrolactone in a dose dependent manner.

The compounds of formula I are therefore indicated for use as antipsychotic agents, for example for the treatment of schizophrenia. An indicated daily dosage is in the range from about 0.01 to about 1 mg, conveniently given in divided doses 2 or 4 times a day in unit dosage form containing from about 0.0025 mg to about 0.5 mg of the compounds admixed with a solid or liquid pharmaceutical carrier or diluent.

The preferred indication is the anti-parkinson indication.

The compounds (4S,5aR)-5-ethyl-4,5,5a,6-tetrahydro-9,10-dihydroxy-4-*n*-propyl-dibenz[cd,f]indole, (4S,5aR)-4-ethyl-4,5,5a,6-tetrahydro-9,10-dihydroxy-5-*n*-propyl-9,10-dihydroxy-dibenz[cd,f]indole, (4S,5aR)-4,5-diethyl-4,5,5a,6-tetrahydro-9,10-dihydroxy-dibenz[cd,f]indole and (4S,5aR)-4,5,5a,6-tetrahydro-9,10-dihydroxy-4,5-di-*n*-propyl-dibenz[cd,f]indole and the corresponding di-*n*-propionyl- and di-isobutyrylester-derivatives are the preferred compounds.

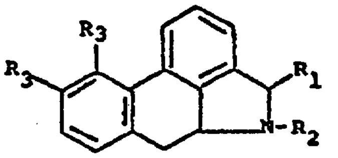
The compounds of formula I may be administered in pharmaceutically acceptable acid addition salt form. These salt forms exhibit the same order of activity as the free base forms.

The present invention also provides a pharmaceutical composition comprising a compound of formula I, in free base form or in pharmaceutically acceptable acid addition salt form, in association with a pharmaceutically acceptable diluent or carrier.

These compositions may be formulated in conventional manner so as to be, for example, a solution, a capsule or a tablet.

CLAIMS

1. A process for the production of a compounds of formula I,

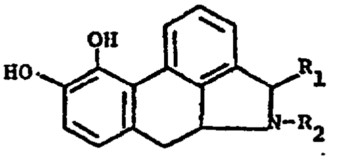


I

wherein

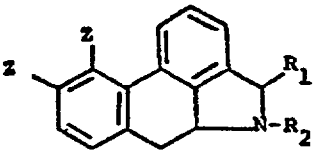
R_1 and R_2 independently, are ethyl or *n*-propyl radicals, and
the R_3 substituents are the same and are hydroxy or acyloxy radicals,
in racemic form having the relative configuration 4R*,5aS*, or in optically active isomer form having the absolute configuration 4S,5aR, which comprises

a) producing a compound of formula Ia



Ia

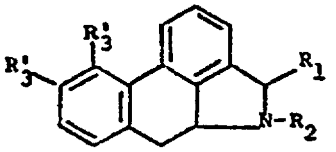
wherein R_1 and R_2 are defined above and Z is a splittable ether group, in racemic form having the



II

wherein R_1 and R_2 are defined above and Z is a splittable ether group, in racemid form having the relative configuration 4R*,5aS*, or in optically active isomer form having the absolute configuration 4S,5aR, or

b) producing a compound of formula Ib



Ib

wherein R_1 and R_2 are defined above and the radicals R_3' are identical acyloxy radicals, by acylating a compound of formula Ia in racemic form having the relative configuration 4R*,5aS* or in optically active isomer form having the absolute configuration 4S,5aR.

2. A process for the production of a compound of formula I defined in Claim 1 substantially as hereinbefore described with reference to any one of the examples 3 to 6.

3. A compound of formula I whenever produced by a process as claimed in Claim 1.

4. A compound of formula I as defined in Claim 1.

5. A compound of Claim 4 wherein each R_3 is hydroxy.

6. A compound of Claim 4 wherein each R_3 is acyloxy.

7. A compound of Claim 6 wherein each acyloxy radical is of formula

$$R_a\text{—CO—O—}$$

wherein R_a is an alkyl radical, (C_{3-7})cycloalkyl, a phenyl radical or a 5- or 6-membered heterocyclic ring.

8. A compound of Claim 7 wherein R_aCOO— is propionyloxy.

9. A compound of Claim 7 wherein R_aCOO— is isobutyryloxy.

10. A compound of any one of Claims 4 to 9 wherein R_1 and R_2 are each ethyl.

11. A compound of any one of Claims 4 to 9 wherein R_1 and R_2 are each *n*-propyl.

12. A compound of any one of Claims 4 to 9 wherein R_1 is ethyl and R_2 is *n*-propyl.

13. A compound of any one of Claims 4 to 9 wherein R_1 is *n*-propyl and R_2 is ethyl.

14. A compound of any one of Claims 4 to 13 in racemic form having the relative configuration 4R*,5aS*.

15. A compound of any one of Claims 4 to 13 in optically active isomer form having the absolute configuration 4S,5aR.

16. (±)-(4R*,5aS*)-5-ethyl-4,5,5a,6-tetrahydro-9,10-dihydroxy-4-*n*-propyl-dibenz[cd,f]indole.

17. (±)-(4R*,5aS*)-4,5-diethyl-4,5,5a,6-tetrahydro-9,10-dihydroxy-dibenz[cd,f]indole.

18. (±)-(4R*,5aS*)-4,5,5a,6-tetrahydro-9,10-dihydroxy-4,5-di-*n*-propyl-dibenz[cd,f]indole.

19. (±)-(4R*,5aS*)-4-ethyl-4,5,5a,6-tetrahydro-9,10-dihydroxy-5-*n*-propyl-dibenz[cd,f]indole

20. (4S,5aR)-5-ethyl-4,5,5a,6-tetrahydro-9,10-dihydroxy-4-*n*-propyl-dibenz[cd,f]indole.

21. (4S,5aR)-4-ethyl-4,5,5a,6-tetrahydro-9,10-dihydroxy-4-*n*-propyl-dibenz[cd,f]indole.

22. (4S,5aR)-4,5-diethyl-4,5,5a,6-tetrahydro-9,10-dihydroxy-dibenz[cd,f]indole.

23. (4S,5aR)-4,5,5a,6-tetrahydro-9,10-dihydroxy-4,5-di-*n*-propyl-dibenz[cd,f]indole.

24. (4S,5aR)-5-ethyl-9,10-dibenzoyloxy-4,5,5a,6-tetrahydro-4-*n*-propyl-dibenz[cd,f]indole.

25. (4S,5aR)-9,10-diacetoxy-5-ethyl-4,5,5a,6-tetrahydro-4-*n*-propyl-dibenz[cd,f]indole.

26. (4S,5aR)-5-ethyl-4,5,5a,6-tetrahydro-4-*n*-propyl-9,10-dipropionyloxy-dibenz[cd,f]indole.

27. (4S,5aR)-9,10-dibutyryloxy-5-ethyl-4,5,5a,6-tetrahydro-4-*n*-propyl-dibenz[cd,f]indole.

28. (4S,5aR)-5-ethyl-4,5,5a,6-tetrahydro-9,10-diisobutyryloxy-4-*n*-propyl-dibenz[cd,f]indole.

29. (4S,5aR)-4,5,5a,6-tetrahydro-9,10-dipropionyloxy-4,5-di-*n*-propyl-dibenz[cd,f]indole.

30. A compound of any one of Claims 4 to 29 in free base form.

31. A compound of any one of Claims 4 to 29 in acid addition salt form.

32. A pharmaceutical composition which comprises a compound of any one of claims 4 to 29, in free base form or in pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent.

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